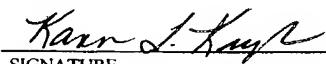


FORM PTO-1390 (REV. 12-2001)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
				11146/11005
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371				U.S. APPLICATION NO. (If known, see 37 CFR 1.5
INTERNATIONAL APPLICATION NO. PCT/US00/25874		INTERNATIONAL FILING DATE 21 September 2000 (21.09.00)		10 / 088713
				PRIORITY DATE CLAIMED 25 September 1999 (25.09.99)
TITLE OF INVENTION VISCOSITY MODULATING SUBSTANCE AND USE THEREOF				
APPLICANT(S) FOR DO/EO/US CARL V. MANION				
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:				
<p>1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.</p> <p>2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.</p> <p>3. <input type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.</p> <p>4. <input type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31).</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))</p> <ul style="list-style-type: none"> a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> has been communicated by the International Bureau. c. <input checked="" type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). <p>6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2))</p> <ul style="list-style-type: none"> a. <input type="checkbox"/> is attached hereto. b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4). <p>7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))</p> <ul style="list-style-type: none"> a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made. <p>8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</p> <p>10. <input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p>				
Items 11 to 20 below concern document(s) or information included:				
<p>11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</p> <p>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input checked="" type="checkbox"/> A FIRST preliminary amendment.</p> <p>14. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.</p> <p>15. <input type="checkbox"/> A substitute specification.</p> <p>16. <input type="checkbox"/> A change of power of attorney and/or address letter.</p> <p>17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.</p> <p>18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4).</p> <p>19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).</p> <p>20. <input type="checkbox"/> Other items or information:</p>				

10/088713

JCT3 Rec'd PTO/PTC 20 MAR 2002

U.S. APPLICATION NO. (if known; see 37 CFR 1.51) 10/088713		INTERNATIONAL APPLICATION NO. PCT/US00/25874	ATTORNEY'S DOCKET NUMBER 11146/11005
21. <input checked="" type="checkbox"/> The following fees are submitted:		CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1040.00			
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$890.00			
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$740.00			
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$710.00			
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00			
ENTER APPROPRIATE BASIC FEE AMOUNT =		\$ 890.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		\$ 130.00	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total claims	14 - 20 =	0	x \$18.00
Independent claims	5 - 3 =	2	x \$84.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)		+ \$280.00	\$
TOTAL OF ABOVE CALCULATIONS =		\$ 1188.00	
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.		\$ 1188.00 (594.00)	
SUBTOTAL =		\$ 594.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).		\$ -0-	
TOTAL NATIONAL FEE =		\$ -0-	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +		\$ -0-	
TOTAL FEES ENCLOSED =		\$ 594.00	
		Amount to be refunded: \$	
		charged: \$	
<p>a. <input type="checkbox"/> A check in the amount of \$ _____ to cover the above fees is enclosed.</p> <p>b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. <u>18-1260</u> in the amount of \$ <u>594.00</u> to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>18-1260</u>. A duplicate copy of this sheet is enclosed.</p> <p>d. <input type="checkbox"/> Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.</p>			
<p>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.</p> <p>SEND ALL CORRESPONDENCE TO: SIDLEY AUSTIN BROWN & WOOD LLP. 717 North Harwood, Suite 3400 Dallas, Texas 75201</p>			
 SIGNATURE Karen L. Knezek NAME <u>39,253</u> REGISTRATION NUMBER			

11146/10204

DT06 Rec'd PCT/PTO 22 JUL 2002

Applicant or Patentee: **Carl V. Manion**

Serial or Patent No.: 10/088,713

Filed or Issued: September 21, 2000

Filed or Issued: September 21, 2001
Attorney's Docket No.: 11146/11905

For: VISCOSITY MODULATING SUBSTANCE AND USE THEREOF

VERIFIED STATEMENT (DECLARATION)

CLAIMING SMALL ENTITY STATUS

(37 C.F.R. §§ 1.9(f) and 1.27(d))

NONPROFIT ORGANIZATION

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

NAME OF ORGANIZATION: Oklahoma Medical Research Foundation

ADDRESS OF ORGANIZATION: 825 NE 13th Street, Oklahoma City, Oklahoma 73104

TYPE OF ORGANIZATION

- () UNIVERSITY OR OTHER INSTITUTE OF HIGHER EDUCATION
 - (X) TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 U.S.C. §§ 501(a) and 501(c)(3))
 - () NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA
 - (NAME OF STATE)
 - (CITATION OF STATUTE)
 - () WOULD QUALIFY AS TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE (26 U.S.C. §§ 501(a) AND 501(c)(3)) IF LOCATED IN THE UNITED STATES OF AMERICA
 - () WOULD QUALIFY AS NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA IF LOCATED IN THE UNITED STATES OF AMERICA
 - (NAME OF STATE)
 - (CITATION OF STATUTE)

**VERIFIED STATEMENT (DECLARATION) CLAIMING
SMALL ENTITY STATUS (37 C.F.R. §§1.9 (f)
AND 1.27 (d)) NONPROFIT ORGANIZATION**

PAGE 1 OF 3

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 C.F.R. § 1.9(e) for purposes of paying reduced fees under §§ 41(a) and (b) of Title 35, United States Code, with regard to the invention entitled **VISCOSITY MODULATING SUBSTANCE AND USE THEREOF** by inventor **Carl V. Manion** described in

- () the specification filed herewith.
(X) PCT International Application No. PCT/US00/25874, filed September 21, 2000 and under 35 U.S.C. §371 as Serial No. 10/088,713
() patent no. , issued .

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization regarding the above-identified invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights in the invention is listed below* and that no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 C.F.R. § 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 C.F.R. § 1.9(d) or a nonprofit organization under 37 C.F.R. § 1.9(e).

Each person, concern or organization having any rights in the invention is listed below:

- (X) no such person, concern or organization
() persons, concerns or organizations listed below*

*NOTE: Separate verified statements are required from each named person, concern, or organization having rights to the invention averring to their status as small entities. (37 C.F.R. § 1.27)

NAME: **N/A**

ADDRESS:

() individual () small business concern () nonprofit organization

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 C.F.R. § 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are

**VERIFIED STATEMENT (DECLARATION) CLAIMING
SMALL ENTITY STATUS (37 C.F.R. §§1.9 (f)
AND 1.27 (d)) NONPROFIT ORGANIZATION**

PAGE 2 OF 3

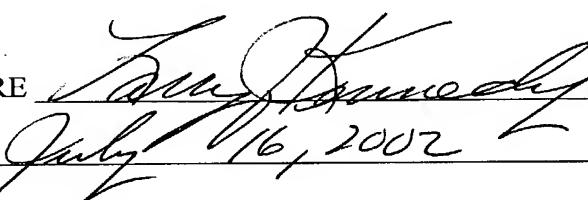
11146/10204

punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: *Larry J. Kennedy*

TITLE IN ORGANIZATION: *Vice-President, Technology Transfer*

ADDRESS OF PERSON SIGNING: **825 Northeast 13th Street**
Oklahoma City, Oklahoma 73104

SIGNATURE 

DATE July 16, 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Carl V. Manion

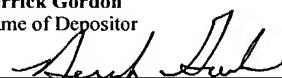
For: **VISCOSITY MODULATING SUBSTANCE
AND USE THEREOF**

Application Serial No. Unassigned

Filing Date: Concurrently herewith

International Application No.: PCT/US00/25874

International Filing Date: 21 September 2000

Assistant Commissioner for Patents
Box PCT
Washington, D.C. 20231EXPRESS MAIL NO. EL861131885US DATE OF DEPOSIT 20 March 2002
I hereby certify that this correspondence is being deposited with the United States
Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10
on the date indicated above and is addressed to the Assistant Commissioner for
Patents, Box PCT, Washington, D.C. 20231 on 20 March 2002
(Date of Deposit)Derrick Gordon
Name of DepositorSignature
Date of Signature: 20 March 2002

Dear Sir:

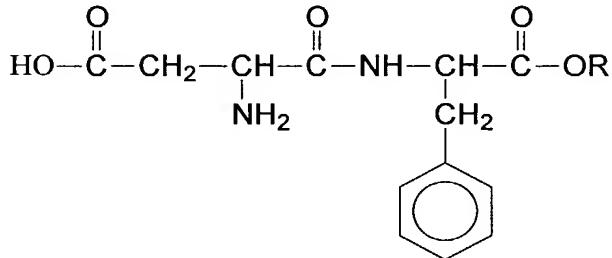
PRELIMINARY AMENDMENT

This preliminary amendment is being filed concurrently with the 35 U.S.C. §371 national stage filing of International Application No. PCT/US00/25874. In accordance with 37 C.F.R. §1.121(c)(3), this document implements changes to the claims by presenting an entire set of pending claims. An Appendix entitled Version With Markings to Show Changes Made is attached showing the current amendments to the claims in marked form. Any claim not accompanied by a marked up version should be construed as not having been changed relative to the immediate prior version thereof, if any.

IN THE CLAIMS

Please replace the previous version of the claims with the following clean version, wherein Claims 1-2 have been deleted, Claims 5 and 14 have been amended, and new Claims 15-16 have been added.

3. A method for treatment of high whole blood viscosity in a patient comprising administering in a treatment regimen to said patient an effective amount of a composition comprising



5 where R is CH₃ or an alkyl, wherein said treatment regimen is capable of reducing whole blood viscosity in said patient.

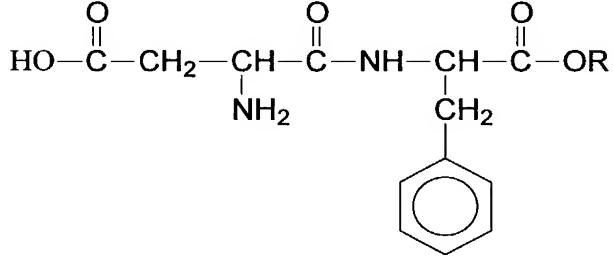
4. The method of Claim 3, wherein said alkyl having 2 to 6 carbons.

5. The method of Claim 3, wherein said effective amount is from about 1 milligram to about 6 milligrams per kilogram body weight.

6. A method for reducing whole blood viscosity in a patient blood sample, comprising the steps of:

a. collecting a blood sample from said patient; and

b. adding to said sample an effective amount of a composition comprising the compound

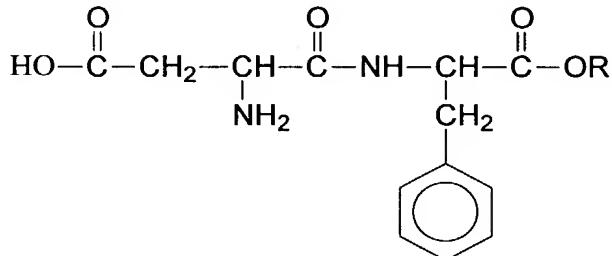


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wherein R is CH₃ or an alkyl, wherein said effective amount causes a reduction in whole blood viscosity.

7. The method of Claim 6, wherein said alkyl having 2 to 6 carbons.

8. A method for monitoring the reduction of whole blood viscosity in a patient receiving treatment with a composition comprising

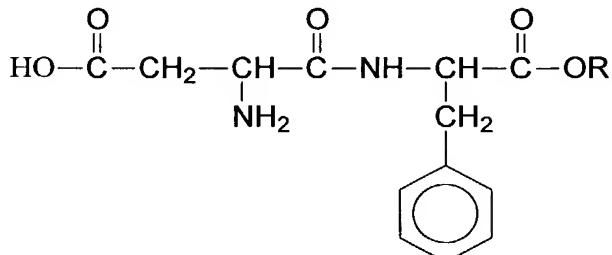


where R is CH₃ or an alkyl of 2 to 6 carbons, comprising:

- 5 a. at a first time point, collecting a blood sample from said patient to form a first patient sample;
- b. measuring the viscosity of said first patient sample to obtain a first viscosity value;
- c. at a second time point, collecting a blood sample from said patient to form a second patient sample;
- 10 d. measuring the viscosity of said second patient sample to obtain a second viscosity value; and
- e. comparing said second viscosity value to said first viscosity value,
 wherein a reduction of viscosity is demonstrated by said second viscosity value being less than said first viscosity value.

9. The method of Claim 8, wherein said viscosity value is determined by drawing an aliquot of said patient sample into a pipette which is in a stationary vertical position and measuring the time required to expel a drop of said patient sample from said pipette using constant pressure to obtain a time interval as said viscosity value.

10. A screening method for determining if a patient's whole blood viscosity can be reduced by a treatment regimen with a composition comprising

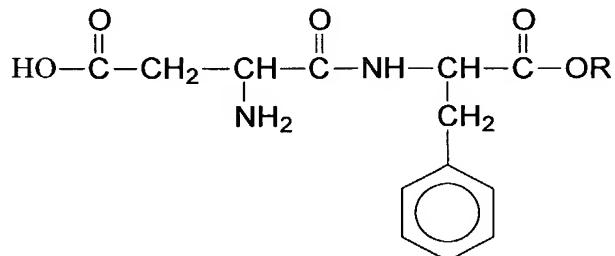


where R is CH₃ or an alkyl of 2 to 6 carbons, comprising:

- 5 a. collecting a blood sample from said patient prior to administration of said composition to form an untreated patient sample;
- b. measuring the viscosity of said untreated patient sample to obtain a baseline viscosity value;
- c. administering to said patient said composition at an amount from about 1 milligram to 10 about 6 milligrams per kilogram body weight;
- d. after administrating said composition to said patient, collecting a blood sample from said patient to form a treated patient sample;
- e. measuring the viscosity of said treated patient sample to obtain a post-treatment viscosity value; and
- 15 f. comparing said post-treatment viscosity value to said baseline viscosity value, wherein said post-treatment viscosity value being less than said baseline time viscosity value demonstrating said composition is capable of reducing whole blood viscosity in said patient and wherein said post-treatment viscosity value being greater than or equal to said baseline viscosity value demonstrating said composition is not capable of reducing whole blood viscosity in said 20 patient.

11. The method of Claim 10, wherein said viscosity value is determined by drawing an aliquot of said patient sample into a pipette which is in a stationary vertical position and measuring the time required to expel a drop of said patient sample from said pipette using constant pressure to obtain a time interval as said viscosity value.

12. A method for treating a patient having a disease characterized by abnormally viscous whole blood comprising administering in a treatment regimen to said patient an effective amount of a composition comprising



5 where R is CH₃ or an alkyl, wherein said treatment regimen is capable of reducing whole blood viscosity in said patient.

13. The method of Claim 12, wherein said alkyl having 2 to 6 carbons.

14. The method of Claim 12, wherein said effective amount is from about 1 milligram to about 6 milligrams per kilogram body weight.

15. The method of Claim 4, wherein said effective amount is from about 1 milligram to about 6 milligrams per kilogram body weight.

16. The method of Claim 13, wherein said effective amount is from about 1 milligram to about 6 milligrams per kilogram body weight.

REMARKS

Prior to this Preliminary Amendment, Claims 1-14 as presented in the annex to the International Preliminary Examination Report were pending. With this Preliminary Amendment, Claims 1-2 drafted in the European Swiss-type use format have been deleted, and Claims 5 and 14 have been amended and new Claims 15-16 added to remove multiple dependency. Applicants respectfully request these changes be entered into the application.

Payment for the fees associated with these claims as amended has been directed on the Transmittal Letter to the United States Designated/Elected Office Concerning a Filing Under 35 U.S.C. §371 filed concurrently herewith.

Respectfully submitted,

By: Karen L. Knezek
Karen L. Knezek
Registration No. 39,253

KLK:FIS

20 March 2002

SIDLEY AUSTIN BROWN & WOOD LLP
717 N. Harwood, Suite 3400
Dallas, Texas 75201
(214) 981-3300
(214) 981-3400 (FAX)

VISCOSITY MODULATING SUBSTANCE AND USE THEREOF**TECHNICAL FIELD OF INVENTION**

The present invention relates to the viscosity modulating effects of N-L-alpha-aspartyl-L-phenylalanine 1-methyl ester, its use in pharmaceutical preparations for the treatment of diseases affected by blood viscosity, and a method of monitoring disease progression.

BACKGROUND OF THE INVENTION

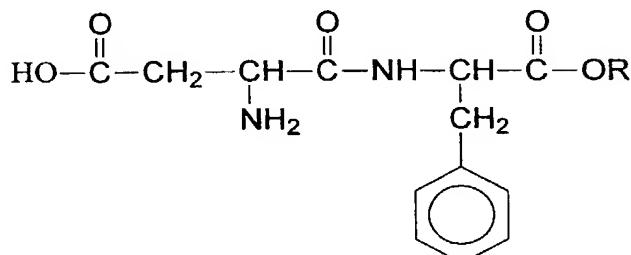
In the body, whole blood viscosity increases as the blood flow through the capillaries decreases. Decreased blood flow can result from elevated levels of circulating blood cells, aggregation of blood cells, distortion of blood cell shape such as the sickling of red blood cells, elevated levels of circulating immunoglobulins, and gelation of certain types of immunoglobulins such as cryoglobulin. Numerous diseases are known to be associated with decreased blood flow leading to increased blood viscosity, and common symptoms include anemia, severe pain, and thrombotic complications.

Patients suffering from various plasma cell dyscrasias, for example, multiple myeloma, primary or Waldenström's macroglobulinemia, and certain heavy chain diseases which clinically mimic multiple myeloma routinely exhibit increased blood viscosity. These diseases are often associated with various dysproteinemias caused by overproduction of monoclonal immunoglobulins including markedly elevated plasma IgM concentrations and cryoglobulinemia. Systemic lupus erythematosus (lupus; SLE) and arthritis are also associated with similar dysproteinemias, and patients may exhibit increased whole blood viscosity.

Whole blood viscosity is often increased during complications in sickle cell disease. Under low oxygen tension, sickle cell deoxyhemoglobin (HbS) forms multi-stranded fibers (Rodgers, et al. 1987. *Proc Natl Acad Sci USA* 84:6157-6161; Eaton, 25 W.A. and Hofrichter, J. 1990. *Adv Protein Chem* 40:63-279) that force a red blood cell (RBC) into a crescent, or sickle, shape. Physiologically, decreased hemoglobin concentration associated with sickled RBCs impair blood flow, resulting increased whole blood viscosity.

Preventive treatment for these diseases is unknown, and therapy is symptomatic. Sickle cell and multiple myeloma patients are treated with hydration, analgesics for pain relief, and exchange transfusion for severe cases of anemia. Chemotherapy utilizing alkylating agents and corticosteroids is prescribed to multiple myeloma patients and 5 macroglobulinemia patients. For hyperviscosity in macroglobulinemia patients, plasmapheresis is commonly practiced. Therapy for SLE and arthritis includes analgesics, arthralgias, and corticosteroids.

U.S. Patent No. 5,654,334 discloses a method for decreasing pain comprising administering N-L-alpha-aspartyl-L-phenylalanine 1-methyl ester (APM) and certain 10 derivatives having the following structure



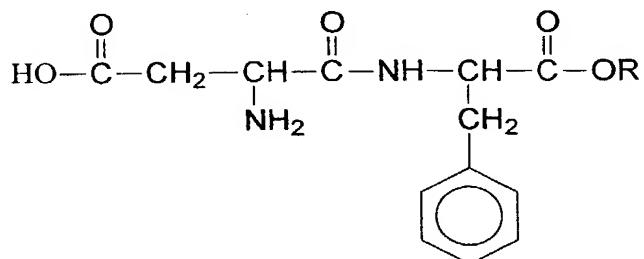
wherein R is H or an alkyl having 1-6 carbon atoms, as a pain reliever which is especially effective in relieving pain associated with osteoarthritis and multiple sclerosis. Further, International Application WO 97/00692 discloses a pharmaceutical preparation for 15 administration to obtain an analgesic effect comprising APM derivatives wherein R is H or an alkyl containing 2 to 6 carbons as well as the antipyretic effect of APM and its derivatives. In a clinical trial, APM was demonstrated to alleviate the pain and inflammation of osteo- and mixed osteo- and rheumatoid arthritis by an unknown mechanism (Edmundson, A.B. and Manion, C.V. 1998. *Clinical Pharmacology and 20 Therapeutics* 63:580-593).

International Application WO 00/18418 discloses a pharmaceutical preparation comprising APM or one of its derivatives wherein R is an alkyl useful in obtaining an antisickling effect in red blood cells. The application discloses that APM interacts with the HbS molecule to the extent that the stacking of the HbS molecules within the red 25 blood cell is significantly altered, leading to a reduction in the capacity of red blood cells containing HbS to sickle with hypoxemia.

It has now been found that APM lowers whole blood viscosity in vivo, resulting in a viscosity modulating agent useful in the treatment of diseases of interest. A method of monitoring the progression of disease based on whole blood viscosity has also been found.

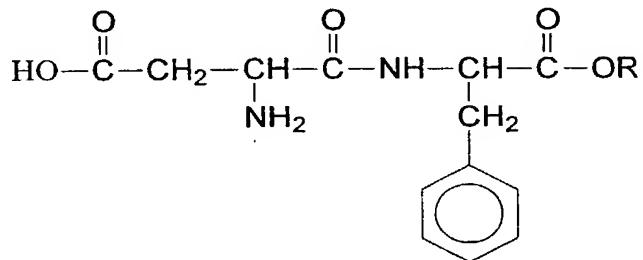
5 SUMMARY OF THE INVENTION

In one aspect, the present invention is use of the compound



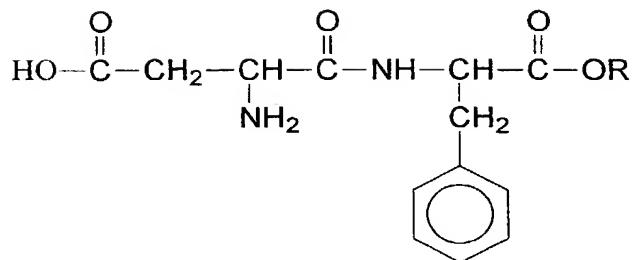
where R is CH₃ or an alkyl to prepare a pharmaceutical composition useful for effecting a reduction in whole blood viscosity in a mammal. Preferably, the alkyl has 2 to 6 carbons.

10 In another aspect, the present invention is a pharmaceutical preparation in dosage unit form adapted for administration to obtain a reduction in whole blood viscosity, comprising, per dosage unit, an effective, nontoxic amount of a compound comprising



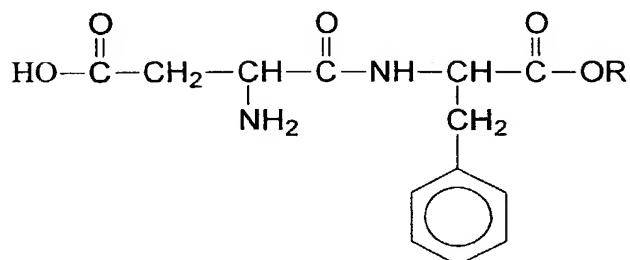
15 wherein R is CH₃ or an alkyl and a pharmaceutical carrier. Preferably, the alkyl has 2 to 6 carbons. A preferred dosage is from about 1 milligram to about 6 milligrams per kilogram body weight.

In another aspect, the present invention is a method for treatment of high whole blood viscosity in a patient comprising administering in a treatment regimen to said patient an effective amount of a composition comprising



where R is CH₃ or an alkyl, wherein said treatment regimen is capable of reducing whole blood viscosity in the patient. Preferably, the alkyl has 2 to 6 carbons. A preferred effective amount is from about 1 milligram to about 6 milligrams per kilogram body weight.

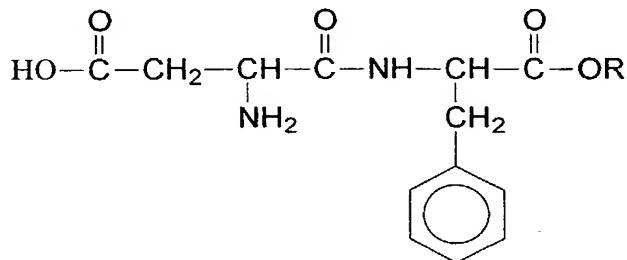
In another aspect, the present invention is a method for reducing whole blood viscosity in a patient blood sample, comprising collecting a blood sample from the patient; and adding to the collected blood sample an effective amount of a composition comprising the compound



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wherein R is CH₃ or an alkyl, wherein the effective amount causes a reduction in whole blood viscosity. Preferably, the alkyl has 2 to 6 carbons.

In another aspect, the present invention is a method for monitoring the reduction of whole blood viscosity in a patient receiving treatment with a composition comprising

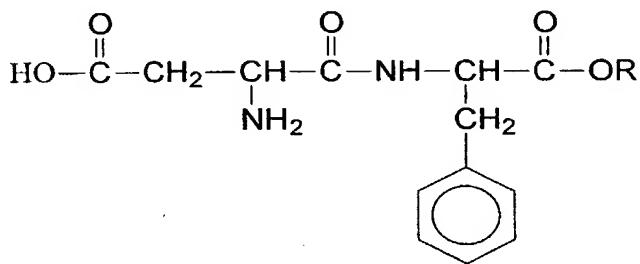


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where R is CH₃ or an alkyl having 2 to 6 carbons comprising: (a) at a first time point, collecting a blood sample from the patient administration of the composition to form a

first patient sample; (b) measuring the viscosity of the first patient sample to obtain a first viscosity value; (c) at a second time point, collecting a blood sample from the patient to form a second patient sample; (d) measuring the viscosity of the second patient sample to obtain a second viscosity value; and (e) comparing the second viscosity value to the first viscosity value, wherein a reduction of viscosity is demonstrated by the second viscosity value being less than the first viscosity value. In a preferred embodiment, the first and second viscosity values are determined by drawing an aliquot of each patient sample into a pipette which is in a stationary vertical position and measuring the time required to expel a drop of the patient sample from the pipette using constant pressure to obtain a time interval as the viscosity value.

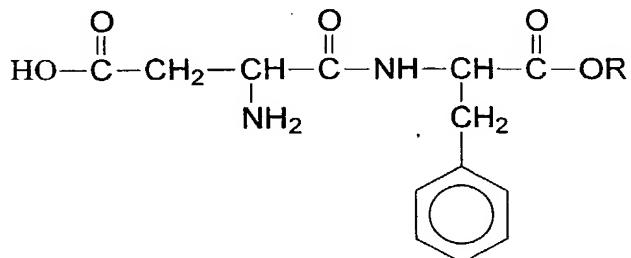
In yet another aspect, the invention is a screening method for determining if a patient's whole blood viscosity can be reduced by a treatment regimen with a composition comprising



where R is CH_3 or an alkyl of 2 to 6 carbons, comprising (a) collecting a blood sample from the patient prior to administration of the composition to form an untreated patient sample; (b) measuring the viscosity of the untreated patient sample to obtain a baseline viscosity value; (c) administering to the patient the composition at an amount from about 1 milligram to about 6 milligrams per kilogram body weight; (d) after administrating the composition to the patient, collecting a blood sample from the patient to form a treated patient sample; and (e) measuring the viscosity of said treated patient sample to obtain a post-treatment viscosity value; and (f) comparing the post-treatment viscosity value to the baseline viscosity value, wherein the post-treatment viscosity value being less than the baseline viscosity value demonstrating the composition is capable of reducing whole blood viscosity in the patient and wherein the post-treatment viscosity value being greater than or equal to the baseline viscosity value demonstrating the composition is not capable of reducing whole blood viscosity in the patient. In a preferred embodiment, the first and

second viscosity value are determined by drawing an aliquot of each patient sample into a pipette which is in a stationary vertical position and measuring the time required to expel a drop of the patient sample from the pipette using constant pressure to obtain a time interval as the viscosity value.

5 In yet another aspect, the invention is a method for treating a patient having a disease characterized by abnormally viscous whole blood comprising administering in a treatment regimen to the patient an effective amount of a composition comprising



10 where R is CH₃ or an alkyl, wherein the treatment regimen is capable of reducing whole blood viscosity in the patient. Preferably, the alkyl has 2 to 6 carbons. A preferred effective amount is from about 1 milligram to about 6 milligrams per kilogram body weight.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph depicting the viscosity measurements for each of the ten patient samples taken at baseline and 120 minutes post-APM administration. The first grouping is the concurrent measurement of the viscosity of water at the time and conditions under which the patient's blood sample was tested; the second grouping is the concurrent measurement of the viscosity of saline at the time and conditions under which the patient's blood sample was tested; the third grouping is the viscosity measurement for each patient taken at baseline (Time 0); and the fourth grouping is the viscosity measurement for each patient taken at 120 minutes post-treatment. In each grouping, the bars appear from left to right in the same order as the listings in the legend presented from top to bottom. The patients identified as TM, BB, and CH whose data is given in the respective 5th, 6th and 7th bar from the left in each treatment group had HgbSC, or SC disease. The patient identified as TC whose data is given in the 4th bar from the left in

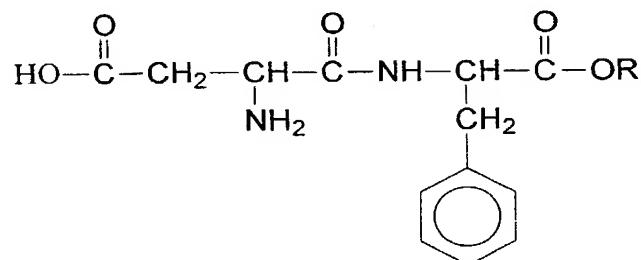
each treatment group had sickle cell disease. The other patients had sickle cell disease, or SS disease.

Fig. 2 is a graph depicting the viscosity measurements for each of the ten patient samples taken at 480 minutes post-in vivo APM treatment after the in vitro addition of 0, 1 milligram, or 2 milligrams of APM per milliliter. The first grouping was viscosity readings for patient samples measured at 480 minutes post-treatment to which no in vitro addition of APM was made; the second grouping was viscosity readings for patient samples measured at 480 minutes post-treatment to which 1 milligram per milliliter APM was added in vitro; and the third grouping was viscosity readings for patient samples measured at 480 minutes post-treatment to which 2 milligram per milliliter APM was added in vitro. In each grouping, the bars appear from left to right in the same order as the listings in the legend presented from top to bottom. The patients identified as TM, BB, and CH whose data is given in the respective 5th, 6th and 7th bar from the left in each treatment group had Hgbsc, or SC disease. The patient identified as TC whose data is given in the 4th bar from the left in each treatment group had sbthal disease. The other patients had sickle cell disease, or SS disease.

Fig. 3 is a graph depicting the correlation of sickle cell count to viscosity, demonstrating a linearly proportional correlation, i.e., as the number of sickle cells per total number of cells counted increases, viscosity also increases.

20 DETAILED DESCRIPTION

It has now been found that N-L-alpha-aspartyl-L-phenylalanine 1-methyl ester (APM) and certain derivatives having the structure of



wherein R is CH₃ or an alkyl, preferably a alkyl of 2 to 6 carbons, lowers whole blood viscosity in vivo and in vitro, providing for the first time a means by which elevated

blood viscosity can be altered. Upon treatment with an effective amount of APM, symptoms and the resultant risks associated with high whole blood viscosity are lessened for patients suffering from one of the diseases of interest.

It is to be understood that the term "APM" used herein refers to N-L-alpha-
5 aspartyl-L-phenylalanine 1-methyl ester and/or one of its derivative having the structure
given above wherein R is an alkyl. An effective amount of APM which can effect a
reduction in whole blood viscosity is from about 1 milligram to about 6 milligrams per
kilogram body weight. A preferred range is from about 3 milligrams to about 6
milligrams per kilogram body weight. Most preferred is about 6 milligrams per kilogram
10 body weight. The dosage can be repeated over time for continued relief, preferably at 6
milligrams per kilogram body weight every 12 hours.

APM can be administered orally, parenterally, intraperitoneally, or sublingually.
It can be administered via ingestion of a food substance containing APM in a volume
sufficient to achieve therapeutic levels. Alternatively, it can be enclosed in capsules,
15 compressed into tablets, microencapsulated, entrapped in liposomes, in solution or
suspension, alone or in combination with a substrate immobilizing material such as starch
or poorly absorbable salts. Pharmaceutically compatible binding agents and/or adjuvant
materials can be used as part of a composition. Tablets or capsules can contain any of the
following ingredients, or compounds of similar nature: a binder such as microcrystalline
20 cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose; an integrating
agent such as alginic acid; corn starch; a lubricant such as magnesium stearate; a glidant
such as colloidal silicon dioxide; and additional sweetening and flavoring agents. When
a capsule form is used the liquid carrier such as a fatty oil may be used. Capsules and
tablets can be coated with sugar, shellac and other enteric agents as is known. APM can
25 also be in a controlled-release formulation or by any controlled-release mechanical means
known in the art.

With the exception of patients suffering from phenylketonuria, APM is
considered as a GRAS (generally regarded as safe) substance. APM is commercially
available, e.g., as ASPARTAME™ (G.D. Searle & Company, Chicago, IL). Its
30 preparation is also disclosed in U.S. Patent No. 3,492,131. While APM is preferred, it is
believed that derivatives of APM can also be used as viscosity modulating agents.

Exemplary derivatives include but are not limited to the ethyl, propyl and butyl esters, and the derivatives should maintain the sweetening property of the dipeptide. Such derivatives, which can be determined using the monitoring methods provided in the examples below, are considered to fall within the scope of this invention.

5 An in vitro method has also been found by which the effectiveness of APM treatment for lowering blood viscosity can be monitored. The method presented in Example 1 uses blood samples taken from patients suffering from sickle cell disorders. The same method would be utilized for blood samples from other diseases of interest. It is to be understood that the examples below are representative of the invention and are 10 intended to be illustrative of the invention, but are not to be construed to limit the scope of the invention in any way. Modifications may be made in the structural features of the invention without departing from the scope of the invention. It will be readily apparent to those skilled in the art that alternative materials methods may also be utilized without departing from the scope of the invention. In particular, the method for measuring 15 viscosity of the whole blood presented in Example 1 is merely representative and any method known in the art for measuring the viscosity of whole blood can be used in the present invention.

Example 1: Viscosity Screening Method for APM Efficacy in Sickle Cell Patients

20 The efficacy of APM treatment can be monitored by measuring the viscosity of patient blood samples before and after treatment. Normal blood viscosity increases with increasing hemoglobin concentration. While patients with sickle cell disease are anemic, the viscosity of their blood appears in the abnormal range, and the viscosity increases with an increase in the number of sickle cells relative to the number of normal cells as the anemia is corrected.

25 Blood samples were obtained from ten patients having homozygous HgBss disease or heterozygous Hgbsc disease before and after a blinded administration of APM at 1.5 (low dose), 3 (medium dose), or 6 (high dose) milligrams per kilogram body weight. Table I gives the patients' characteristics.

TABLE I: Patient Characteristics

No.	Age	Sex	Disease ^a	Hgb	Hct	Dose ^b
TD	13	M	ss	7.6	25.4	H
AH	11	F	ss	8.1	23.3	M
JC	13	M	sbthal	7.5	25.1	L
TC	9	F	sbthal	7.9	25.6	H
JU	4	M	ss	7.9	22.6	M
LJ	4	M	ss	7.9	22.6	H
TM	19	F	sc	10.3	30.2	L
BB	39	F	sc	11.5	39.0	H
CH	52	F	sc	8.0	26.0	M
LW	3	F	ss	7.4	24.0	M
	16.7	3M/5F	ss5/sc3	8.52	26.64	

^a ss = homozygous HgBss; sc = heterozygous HbS and HbC; sbthal = homozygous HbS with -thalassemia.

^b H = high dose, 6 mg/kg body weight; M = medium dose, 3 mg/kg body weight; L = low dose, 1.5 mg/kg body weight.

For comparative purposes, the number of sickle cells relative to the number of normal cells was obtained at 0, 30, 60, 120, 240, 480, and 1440 minutes after administration of APM according to the method given in Example 2.

Viscosity determinations using the RBC pipette method of Wright and Jenkins (1970, *Blood* 36:516) were made on each blinded whole blood sample before and 120 minutes after blinded administration of APM. Each measurement was made in triplicate. Control viscosity measurements using saline and water for each patient and normal whole blood were also made to validate the viscosity measurements.

To measure viscosity, 1.01 cc of the test fluid, i.e., either water, saline or blood, was drawn into an RBC pipette using a 50 cc syringe attached via rubber tubing to the top of the RBC pipette. Using a constant pressure of 20 mm by maintaining the pressure with visual feedback and hand pressure, the amount of time it took for the test fluid to drip out of the RBC pipette was measured with a stopwatch. Each measurement was made in triplicate. Changes in viscosity from baseline for patient blood samples were recorded and compared to normal controls.

The results of the study obtained by this viscosity monitoring method comparing viscosity measurements obtained at baseline and 120 minutes post-treatment are given in Fig. 1 and summarized in Table II. Of the five patients identified as HgBss (homozygous for HbS), blood viscosity decreased after treatment over time. For the two patients 5 diagnosed as sbthal (homozygous HbS with β -thalassemia chain), blood viscosity also decreased after treatment over time, resembling the results obtained with HgBss. In contrast, blood samples taken from three patients diagnosed as Hgbsc (heterozygous HbS and HbC) showed increased viscosity after treatment over time. According to this data, this method of monitoring can be used to delineate "sickle cell disease" from certain 10 "sickle cell trait" disorders, e.g., Hgbsc. The viscosity data was also compared against Pirofsky's change in viscosity vs. hematocrit standard, and the results were that the viscosity decreased in blood samples from patients with sickle cell disease (HgBss) and increased in blood samples from patients with sickle cell trait (Hgbsc).

Table II: Viscosity Results

No. of Patients	Viscosity change	HgBss	sbthal	Hgbsc
7	decreasing	5	2	
3	increasing			3

15

Samples with high viscosity readings at 480 minutes or 1,440 minutes post-treatment, chosen to represent patients with a validated response to APM who were returning to normal, were divided and treated with an additional 0, 1, or 2 20 milligrams/milliliter APM in vitro, in an effort to measure whether a second inducible sickling response was possible and if a second response to the in vitro APM addition could be observed. The viscosity of each sample at 480 minutes post-treatment was measured. As presented in Fig. 2, the viscosity of the blood samples from the patients classified as HgBss decreased over time when compared to the control. In contrast, blood 25 samples from the Hgbsc patients showed an increase in viscosity over time compared to the control.

Baseline and 120 minute post-treatment viscosity measurements were compared with the number of sickle cells relative to the number of normal cells for correlation. The results as presented in Fig. 3 demonstrate that as the number of sickle cells relative to the

number of normal cells increased, the blood viscosity also increased in an essentially linearly proportional correlation.

In summary, APM given orally reduces the number of sickle cells in HgBss blood and also reduces the viscosity of HgBss blood. The addition of APM in vitro also 5 reduces the number of sickle cells in HgBss blood and the viscosity of HgBss blood. The Hgbsc blood was not affected by APM in vivo or in vitro.

The method disclosed herein was effective in providing a means whereby changes in viscosity were determinable for both in vivo and in vitro APM treatment. By 10 measuring changes in viscosity of a patient sample upon in vitro addition of APM, this method can be applied to screen patients to determine their susceptibility to effective APM treatment in vivo. Once on APM treatment, the method can be applied to monitoring changes in viscosity as an indicator of the patient's response to therapy.

Example 2: Metabisulfite Slide Test to Measure Sickling in Blood Samples In Vitro

15 Using the sickling test described herein, the number of sickle cells relative to the number of normal cells can be measured with and without APM treatment.

Blood was drawn before and 120 minutes after treatment with 0, 1.5, 3, or 6 milligrams APM per kilogram body weight in a blinded fashion from the ten patients into heparin tubes, stored in a refrigerator at approximately 10°C and routinely tested within 20 36 hours of collection.

Normal blood devoid of abnormal hemoglobin was used as a control. For each heparinized patient blood sample and the normal blood control, experimental samples were prepared containing 0.25 milliliters of normal saline and 0.25 milliliters of blood.

Using metabisulfite to reduce HbS to the deoxy form (Daland, G.A. and Castle, 25 W.B. 1948. *J Lab Clin Med* 33:1082-1088; Nelson, D.A. In Todd-Sanford-Davidsohn *Clinical Diagnosis by Laboratory Methods*, J.B. Henry, ed. (W.B. Saunders Co., Philadelphia, 1979, vol. 1, p. 1020), a baseline sickling test was run on each experimental sample. The sickling inducing agent was prepared fresh daily as follows: 10 milligrams metabisulfite in 1 milliliter isotonic saline. Multiple test slides were prepared for each 30 experimental sample by adding approximately 300 microliters of the metabisulfite

inducing agent to 50 microliters of well mixed blood and placing about 4 drops of the experimental sample onto the surface of a glass slide, placing a coverslip over the sample, and sealing the coverslip with a petroleum jelly bead to prevent oxygen from entering the sample. Triplicate counts were made manually of the number of sickle cells and normal cells, and the results were recorded as the number of sickle cells per 100 cells counted.

Photomicrographs were also taken with a phase contrast microscope at 400 magnification, and the results were obtained from the photomicrographs as the number of sickle cells per 100 cells counted using a ScanPro scanner and software (SigmaScan, Jandel Scientific, San Rafael, CA). The manual counts correlated well with the scanned counts.

To account for natural or non-induced sickling of the experimental samples, a baseline sickling count was obtained for each heparinized patient blood sample and the normal blood control. Slides were prepared by adding 3 drops saline and 1 drop of the experimental sample onto the surface of a glass slide, placing a coverslip over the sample, and sealing the coverslip with a petroleum jelly bead to prevent oxygen from entering the sample. Photomicrographs were taken with a phase contrast microscope at 400 magnification, and the results were obtained from the photomicrographs as the number of sickle cells per 100 cells counted. This number of sickle cells per 100 cells counted was considered the baseline sickling count and was subtracted from the cell counts obtained with the metabisulfite induced samples.

After baseline counts were made, all experimental and control samples were stored in a refrigerator at 10°C between each time point. Metabisulfite slides were subsequently prepared as given above at 30, 60, 120, 240, 480, and 1,440 minutes post administration, and the results were recorded as the number of sickle cells per 100 cells counted.

Example 3: Method of Monitoring Therapy in a Multiple Myeloma Patient

The following method can be used for monitoring the reduction in whole blood viscosity in a patient suffering from multiple myeloma and exhibiting elevated whole blood viscosity upon administration of a composition comprising N-L-alpha-aspartyl-L-phenylalanine 1-methyl ester (APM). A blood sample from the patient is collected prior to treatment with APM. Saline, water, and normal whole blood is used as controls, and

viscosity measurements are taken for saline, water, normal whole blood, and the patient blood with and without APM. To perform each viscosity measurement, an aliquot of the test fluid, i.e., water, saline, normal whole blood, or untreated patient blood is drawn into a pipette held stationary in a vertical position, and the time required to expel a drop of the test fluid from the lower end of the pipette is measured, providing a baseline time interval which serves as an indicator of blood viscosity. Preferably, a constant pressure of about 20 mm is applied to the upper end of the pipette at the time the measurement is taken.

5 After administration of APM to the patient, a second blood sample is collected from the patient. Saline, water, and normal whole blood is used as controls, and viscosity measurements are taken for saline, water, normal whole blood, and the patient blood with and without APM. To perform each viscosity measurement, an aliquot of the test fluid, i.e., water, saline, normal whole blood, or untreated patient blood is drawn into a pipette held stationary in a vertical position, and the time required to expel a drop of the test fluid from the lower end of the pipette is measured, providing a post-treatment time interval

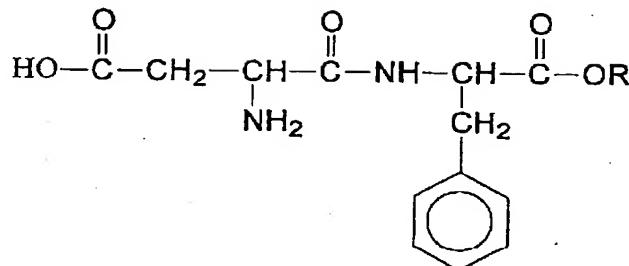
10 which serves as an indicator of blood viscosity. Preferably, a constant pressure of about 20 mm is applied to the upper end of the pipette at the time the measurement is taken.

15 The post-treatment time interval is then compared to the baseline time interval, and a reduction of whole blood viscosity is demonstrated when the post-treatment time interval is less than the baseline time interval.

ART 34 AMDT

I CLAIM:

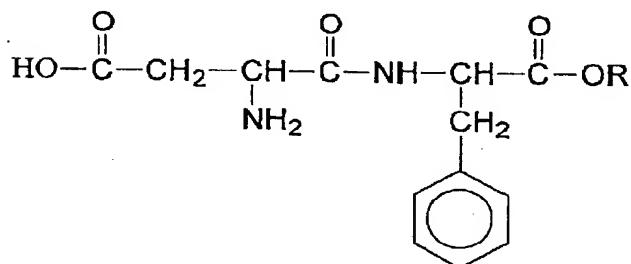
1. Use of the compound



where R is CH₃ or an alkyl to prepare a pharmaceutical composition useful for effecting a reduction in whole blood viscosity in a mammal.

2. The use of Claim 1, wherein said alkyl having 2 to 6 carbons.

3. A method for treatment of high whole blood viscosity in a patient comprising administering in a treatment regimen to said patient an effective amount of a composition comprising



5 where R is CH₃ or an alkyl, wherein said treatment regimen is capable of reducing whole blood viscosity in said patient.

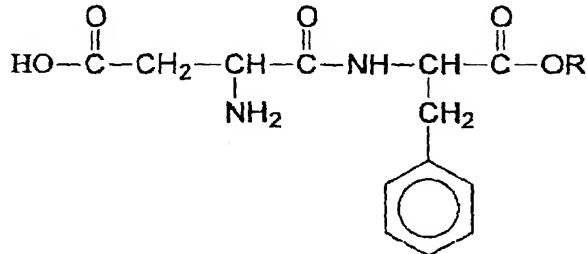
4. The method of Claim 3, wherein said alkyl having 2 to 6 carbons.

5. The method of Claim 3 or 4, wherein said effective amount is from about 1 milligram to about 6 milligrams per kilogram body weight.

ART 34 AMDT

6. A method for reducing whole blood viscosity in a patient blood sample, comprising the steps of:

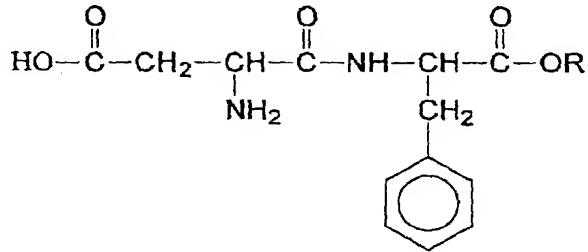
- a. collecting a blood sample from said patient; and
- b. adding to said sample an effective amount of a composition comprising the
5 compound



wherein R is CH₃ or an alkyl, wherein said effective amount causes a reduction in whole blood viscosity.

7. The method of Claim 6, wherein said alkyl having 2 to 6 carbons.

8. A method for monitoring the reduction of whole blood viscosity in a patient receiving treatment with a composition comprising



where R is CH₃ or an alkyl of 2 to 6 carbons, comprising:

- 5 a. at a first time point, collecting a blood sample from said patient to form a first patient sample;
- b. measuring the viscosity of said first patient sample to obtain a first viscosity value;
- c. at a second time point, collecting a blood sample from said patient to form a
10 second patient sample;
- d. measuring the viscosity of said second patient sample to obtain a second viscosity value; and

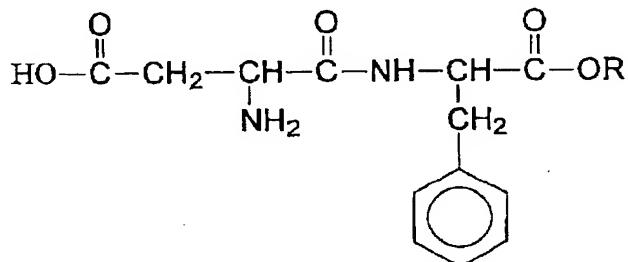
ART 34 AMDT

e. comparing said second viscosity value to said first viscosity value, wherein a reduction of viscosity is demonstrated by said second viscosity value being less than said first viscosity value.

15

9. The method of Claim 8, wherein said viscosity value is determined by drawing an aliquot of said patient sample into a pipette which is in a stationary vertical position and measuring the time required to expel a drop of said patient sample from said pipette using constant pressure to obtain a time interval as said viscosity value.

10. A screening method for determining if a patient's whole blood viscosity can be reduced by a treatment regimen with a composition comprising



where R is CH₃ or an alkyl of 2 to 6 carbons, comprising:

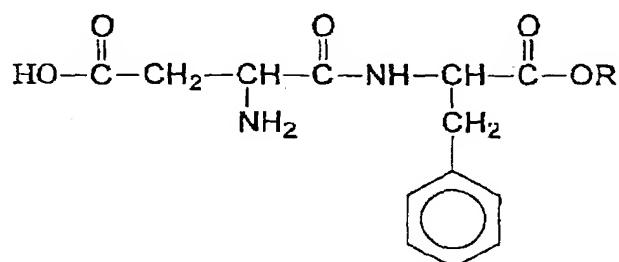
- 5 a. collecting a blood sample from said patient prior to administration of said composition to form an untreated patient sample;
- 10 b. measuring the viscosity of said untreated patient sample to obtain a baseline viscosity value;
- 15 c. administering to said patient said composition at an amount from about 1 milligram to about 6 milligrams per kilogram body weight;
- d. after administrating said composition to said patient, collecting a blood sample from said patient to form a treated patient sample;
- e. measuring the viscosity of said treated patient sample to obtain a post-treatment viscosity value; and
- f. comparing said post-treatment viscosity value to said baseline viscosity value, wherein said post-treatment viscosity value being less than said baseline time viscosity value demonstrating said composition is capable of reducing whole blood viscosity in said patient and wherein said post-treatment viscosity value being greater than or equal to

ART 34 AMEND

20 said baseline viscosity value demonstrating said composition is not capable of reducing whole blood viscosity in said patient.

11. The method of Claim 10, wherein said viscosity value is determined by drawing an aliquot of said patient sample into a pipette which is in a stationary vertical position and measuring the time required to expel a drop of said patient sample from said pipette using constant pressure to obtain a time interval as said viscosity value.

12. A method for treating a patient having a disease characterized by abnormally viscous whole blood comprising administering in a treatment regimen to said patient an effective amount of a composition comprising



5 where R is CH₃ or an alkyl, wherein said treatment regimen is capable of reducing whole blood viscosity in said patient.

13. The method of Claim 12, wherein said alkyl having 2 to 6 carbons.

14. The method of Claim 12 or 13, wherein said effective amount is from about 1 milligram to about 6 milligrams per kilogram body weight.

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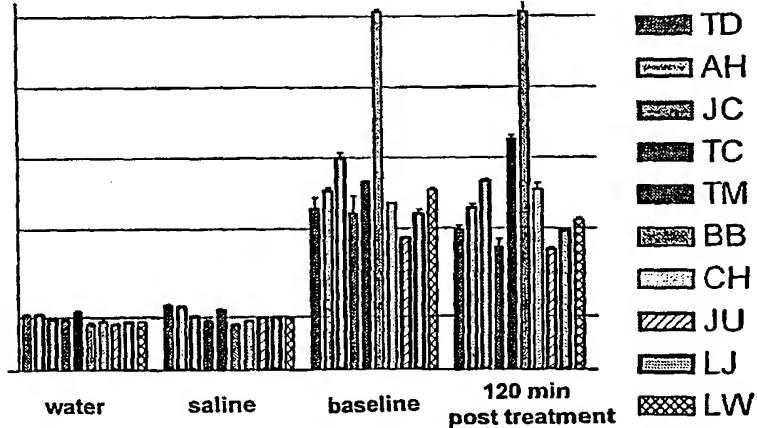
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(54) Title: VISCOSITY MODULATING SUBSTANCE AND USE THEREOF

BASELINE AND 120 MINUTES POST-TREATMENT VISCOSITY MEASUREMENTS



(57) Abstract: It has now been found that N-L-alpha-aspartyl-L-phenylalanine 1-methyl ester (APM) lowers whole blood viscosity in patients, including those suffering from sickle cell disease and plasma cell dyscrasias. Upon in vivo APM treatment, patients experienced a significant lowering of whole blood viscosity. In vitro addition of APM to patients samples having elevated whole blood viscosity resulted in reduced viscosity over time. These in vitro and in vivo results identify APM as a therapeutic agent for molecular diseases which lead to elevated whole blood viscosity. A method by which APM treatment can be monitored is also disclosed.

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BASELINE AND 120 MINUTES POST-TREATMENT VISCOSITY MEASUREMENTS

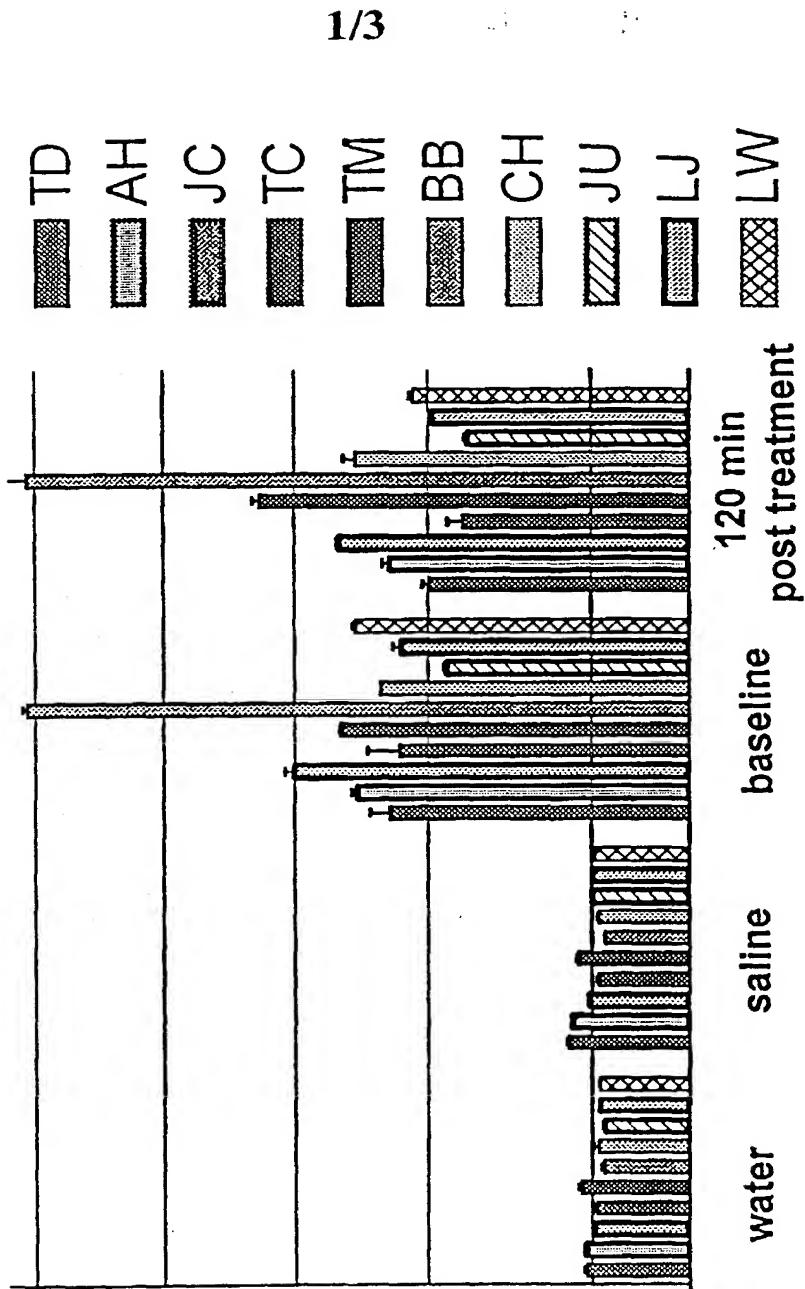


Fig. 1

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CONTROL IN VITRO VISCOSITY

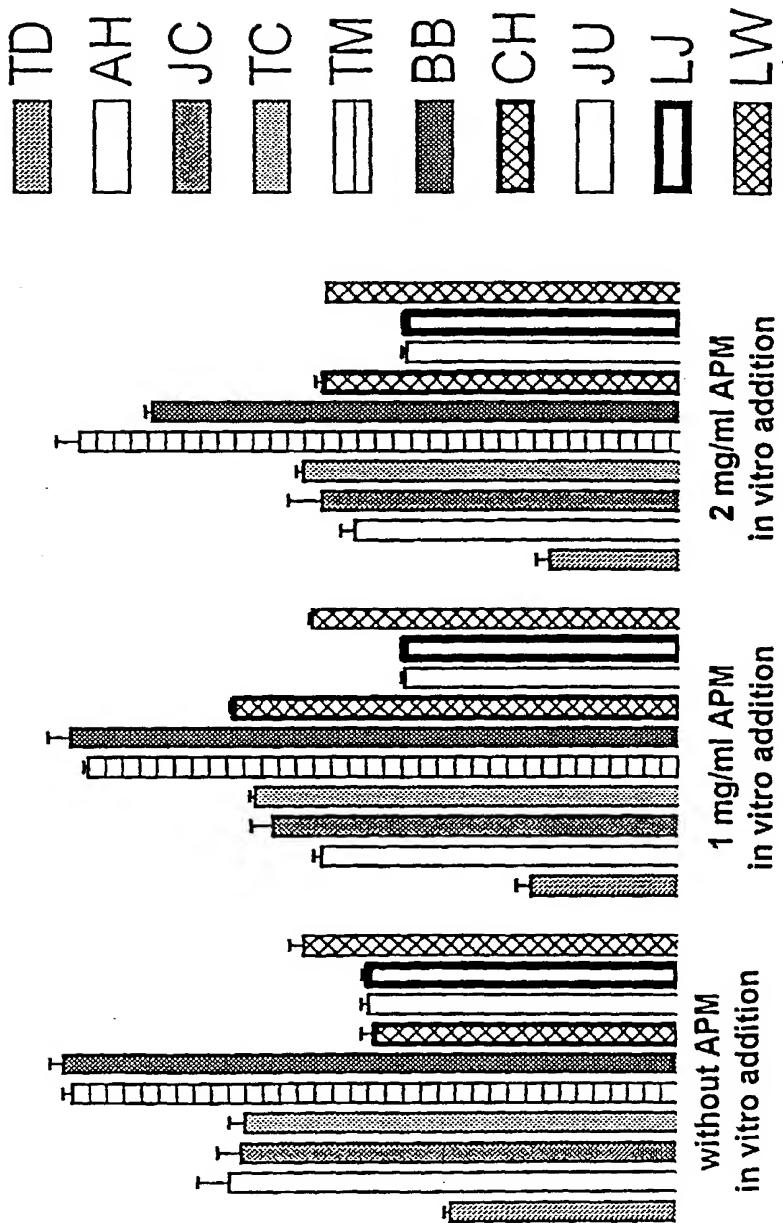


Fig. 2

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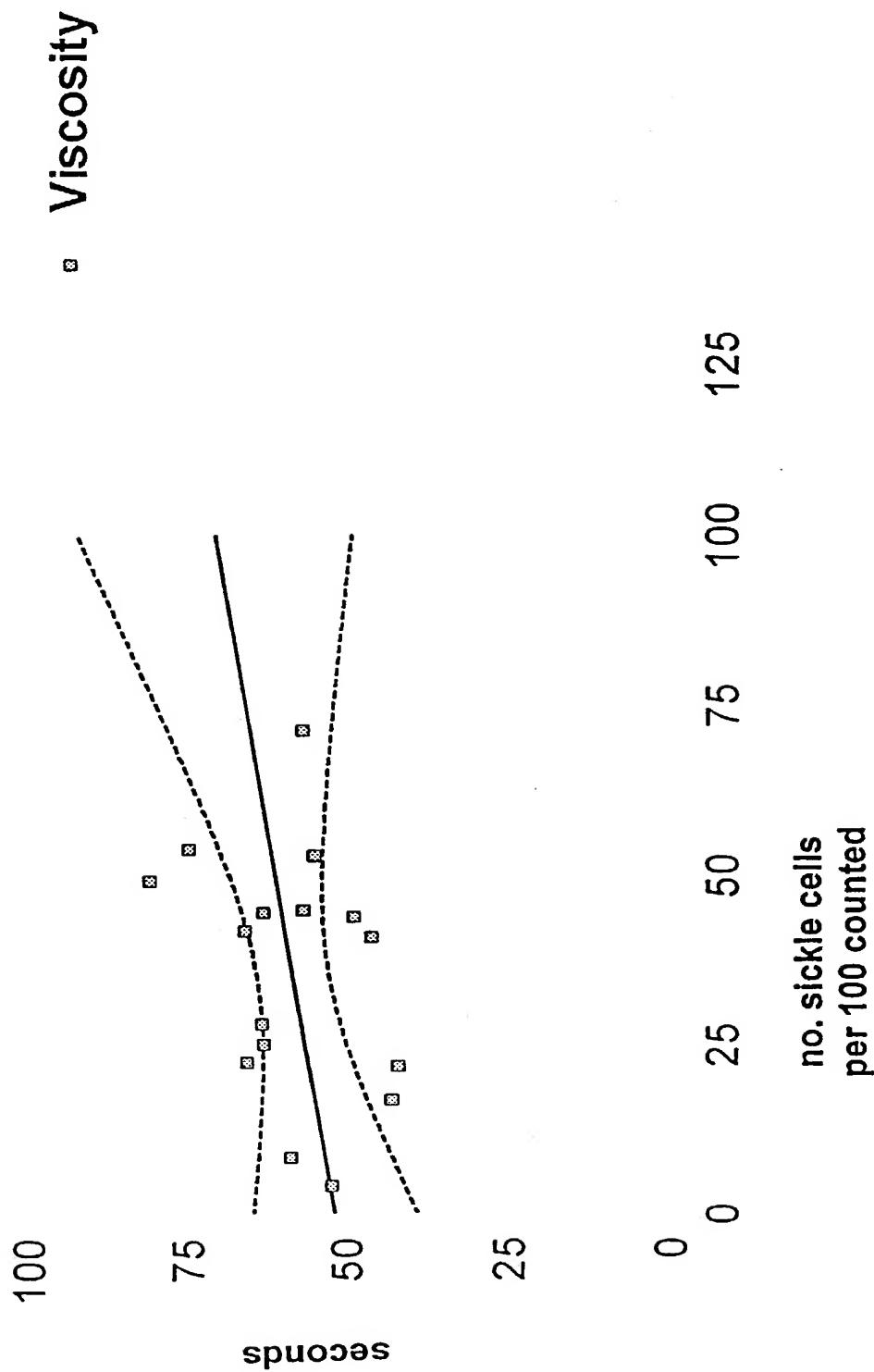


Fig. 3

DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, that I believe that I am the original, first and sole inventor (if only one name is listed below) or I believe that we are the original, first and joint inventors (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention, design or discovery entitled **VISCOSITY MODULATING SUBSTANCE AND USE THEREOF**, the specification of which (check one)

- is attached hereto; or
 was filed on **September 21, 2000**, as PCT International Application Number **PCT/US00/25874** and under 35 U.S.C. §371 as Serial No. **10/088,713**.

that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above; that I do not know and do not believe that said invention, design or discovery was ever known or used in the United States of America before my invention or discovery thereof, or patented or described in any printed publication in any country before my invention or discovery thereof, or more than one year prior to this application, or in public use or on sale in the United States of America more than one year prior to this application; that said invention, design or discovery has not been patented or made the subject of an inventor's certificate issued prior to the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns; and that I acknowledge the duty to disclose information of which I am aware which is material to the examiner of this application in accordance with 37 C.F.R. § 1.56(a).

I hereby claim foreign priority benefits under 35 U.S.C. § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application(s) for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

NUMBER	COUNTRY	DATE FILED	PRIORITY CLAIMED
N/A			

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

APPLICATION SERIAL NO.	DATE FILED
U.S. 60/156,119	September 25, 1999

I hereby claim the benefit under 35 U.S.C. § 120 of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States Application(s) in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. § 1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	DATE FILED	STATUS
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N/A

I hereby appoint:

<u>3</u>	Eugenia S. Hansen	Reg. No. 31,966
	Karen L. Knezek	Reg. No. <u>39,253</u>
	Rod A. Cooper	Reg. No. <u>42,436</u>

all of the firm of Sidley Austin Brown & Wood LLP, my attorneys with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith, and to file and prosecute any international patent applications filed thereon before any international authorities under the Patent Cooperation Treaty.

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Atty. Docket No. **11146/11005**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Full name of sole or joint inventor: Carl V. Manion

Inventor's signature: Carl V. Manion

Date: 6/06/02

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